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09/121,017	07/22/1998	TORU IMAMURA	382.1019	2849

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EXAMINER	
SAUNDERS, DAVID A	

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1644	35

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .	Applicant(s) IMAMURA et al
Examiner SAUNDERS	Group Art Unit 1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 3/29/02, 7/16/02.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1, 3-6, 14, 16-21, 23-28 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1, 3-6, 14, 16-21, 23-28 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 32

☑ Interview Summary, PTO-413 (PAPER 26)

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Following entry of the amendment of 3/29/02 (Paper 31) the claims pending and under examination are 1, 3-6, 14, 16-21, 23-28.

The English language drawings filed on 11/20/98 have been approved by the draftsman.

The amendment of 3/29/02 has overcome the previously stated objection under 37 CFR 1.75© to claim 14.

The amendment has overcome the previously stated rejection of claims 6 and 20 under 35 U.S.C. 112, second paragraph.

New grounds of rejection under 35 U.S.C. 112, second paragraph are stated further herein below.

With respect to the previously stated rejection under 112 first paragraph, regarding new matter in the recitations of "one or more" or a "plurality" of covalently bonded sugar chains the examiner notes the following.

The newly translated specification has not been entered. The amendment of 3/29/02 has no directions for its entry. Even if there had been such directions, the substitute specification would have been objected to under 35 U.S.C. 132 for entry of new matter by reciting "sugar chain(s)". The change is new matter, irrespective of the fact that the priority document may not have been properly translated at the time the original English language specification was filed in the U.S. Ex parte Bondiou 132 USPQ 356.

Nevertheless the new matter rejection regarding recitations of "one or more" or "plurality of" in conjunction with "sugar chains" is withdrawn. Applicant's argument's and exhibits

presented on 3/29/02 are convincing that the peptides added to the heparin binding protein would inherently contain multiple sites at which sugar chains would be added. In like manner it is considered that, if the sugar chains were to be chemically coupled, as described at specification page 15, then there would inherently be multiple amino and/or hydroxyl groups in the heparin binding protein available for such coupling. Such chemical methods do not select for coupling at a particular one of many available functional groups; therefore, coupling of multiple sugar chains to the heparin binding protein would inherently occur.

Thus, though there is no literal support, it is considered that there is inherent support for recitations of "one or more" and "plurality of" in conjunction with "sugar chains".

Applicant's amendment has also overcome the 112 new matter rejection of the independent claims regarding the recitations of "activity" and of claim 20 regarding a "heparin binding protein" comprising a "peptide".

New issues under 112, first paragraph, are stated further below.

Claims 1, 3-6, 14, 16-21 and 23-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, line 2 "being" is extraneous.

Independent claims 1, 16, and 19-20 are each unclear in reciting "the residual activity" for three reasons.

First, it is not clear what kind of "activity" is intended. Is it the heparin binging activity, or is it some other activity of the protein (e.g. the growth promoting activity of FGF)? From what can be gleaned from the disclosure, it appears that the latter is intended.

Second, "residual" is unclear since it is not clear what the "residual activity," is compared against. What is the "baseline" or 100% activity which serves as a comparison standard against which the "residual activity" is compared? It is not even clear as to whether the protein which serves as a comparison standard is glycosylated or not. It appears, from the examples, that applicant may intend the comparison standard is glycosylated.

Third, it is not clear if there is some process or treatment that the protein is subjected to, prior to determining how much "residual activity" remains. From page 5, it appears that applicant might be contemplating some sort of destabilizing process.

In each independent claim the third and fourth members of the Markush group of sugar chains are unclearly recited. In reciting an "O-linked (or N-linked) sugar chain combined with a sulfated polysaccharide or glycosaminoglycan" it is not clear how these are "combined". The examiner can envision two ways: 1) the O-linked sugar chain and the sulfated polysaccharide or glycosaminoglycan are each separately bonded to the protein/peptide, or 2) the O-linked sugar chain is further linked to the sulfated polysaccharide or glycosaminoglycan. (i.e. the sulfated polysaccharide or glycosyamino glycan is indirectly linked to the protein/peptide). The examiner cannot find a description of either embodiment in the original disclosure (see 112 first further infra), thus one has no idea what applicant is claiming.

Independent claim 23 is unclear in reciting "the activity" (lines 5 and 6). As noted supra regarding recitations of "residual activity" it is unclear what kind of "activity" is intended.

For like reasons recitation of "activity" is unclear in claim 6.

Claims 4, 16 and 18-19 are each unclear by reciting "through a peptide". Likewise claim 20 is unclear by reciting "containing a peptide sequence". In each claim it is uncertain how the "peptide" is structurally related to the heparin binding protein; note, in claim 20, "containing a peptide" could be read as part of the amino acid sequence inherent to the structure of the heparin binding protein per se. Otherwise, if it is considered that the "peptide" is a sequence that is added to the heparin binding protein, it is unclear as to how this is added --e.g. fused via a peptide bond, or bridged via a disulfide bond? The disclosure (e.g. pages 7, 9-11) appears to only describe the former case.

The term "near one of the ends" in claim 6 is a relative term which renders the claim indefinite. The term "near one of the ends" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. .

The claims and disclosure give no direction as to how many residues away from the "ends" one can add the sugar chain and still be considered "near" to one of the ends. Also it is not clear if this addition must be at a residue within the heparin binding protein, or if it can be at a residue of a peptide fused thereto.

Claims 5 and 17 are unclear in part (b) by reciting (line 1 thereof) "consists of", which is closed language, and then reciting (line 2) "addition", which is open language.

In claim 17, part (6), line 4, "can be" is unclear because it is not clear whether or not the sugar chain is or is not present.

Claims 18, 20 and 23 are unclear by reciting (line 1) "improved" because the claims fail to specifically point out what feature(s) recited constitute what is "improved". Applicant is referred to 37 CFR 1.75(e) for the proper format of a claim reciting an improvement (Jepson format).

Applicant is advised that should claim 4 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 4, depending from 1, is considered to be a substantial duplicate of independent claim 16, because claim 16 appears to have been written with all of the limitations of both claims 1 and 4.

Claims 1, 3-6, 14-21 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims contain new matter.

In each independent claim the third and fourth members of the Markush group of sugar chain contain new matter. Specifically these were originally recited as simply "an O-linked sugar chain, an N-linked sugar chain", without any recitations of "combined with a sulfated polysaccharide or glycosaminoglycan". There was nothing in the originally filed disclosure that pointed to such a combination of an O- or N-linked sugar chain with a sulfated polysaccharide or glycosaminoglycan. Applicant is therefore greeting a new subspecies of Markush group members that was not originally contemplated.

Claim 23 recites new matter by reciting "wherein the activity of the heparin binding protein is greater than the activity of the unmodified protein". The examiner cannot find any ipsi verbis support for this phrase, and no inherent support. Rather, it appears from page 5 and from the examples that applicant has disclosed that the modified proteins have improved stability over the unmodified proteins.

Newly found prior art is cited herein below.

Claims 1, 3-6, 14, 16-21 and 23-28 are rejected under 35 U.S.C. 102(b) as being entirely anticipated by Saunders et al. (5,486,599).

Saunders et al. disclose heparin binding proteins, such as those of the FGF family, which are expressed as fusion proteins, such that the FGF is fused (at its N-terminal) to a portion of a core peptide known to undergo glycosylation (sugar addition). The sugars which are added to this core peptide include the glycosaminoglycan heparin sulfate. Such fusion (or chimeric) proteins have increased stability ("residual activity") and increased binding activity to for the

growth factor receptor. They teach therapeutic use of such constructs. Thus all features of instant claims 1, 3, 14, 16, 18, 20-21, 24-26 and 28 are clearly anticipated. Applicant is referred to cols. 36-40, most particularly to cols. 38-40 regarding agonistic variants. Applicant is also referred to cols. 60-68 and to claims 15-21.

Regarding claim 6, note that attachment of the glycosaminoglycan sugar chain to the fused are peptide is consistent with the second and third embodiments claimed. By being attached through the are peptide, the sugar chain is attached "near one of the ends" of the heparin binding protein. By being thus attached, the sugar chain does not "cause the protein to incur a loss of activity". See col. 63, for example.

Regarding instant claims 19 and 23, which require the covalent binding of plural sugar chains, note that Saunders et al. teach fusion (chimeric) proteins "comprising "at least one heparin sulfate chain" (col. 38, line 13). Thus the limits of instant claims 19, 23 and dependent claim 27 are within the four corners of the reference. Also, Applicant should note that col. 23, lines 17-21 teach that recombinant peptides containing multiple copies of the recognition sequence (for glycosylation or "sugar chain" attachment) can be prepared. This teaching would provide the enablement required for one to produce fusion proteins having more than one heparin sulfate chain attached thereto.

Regarding claims 5 and 17 reciting SEQ ID NOS: these are considered anticipated for part (b), following the same rational set forth previously regarding Senoo et al. in Paper 18. Therein it was the examiner's position that part (b) of claims 5 and 17 is sufficiently broad as to

the number of deletions, substitutions and insertions that may be provided in the recited SEQ ID NOS: that it is proper to consider these encompassing sequences having the proteoglycan core peptide from the syndecans taught by Saunders et al. For example the ryudocan portion of the instantly recited sequences could be deleted and the core peptide from syndecan, taught by Saunders et al. could be inserted in lieu thereof to provide glycosylation sites.

All claims are thus rejected over the prior art.

Any inquiry concerning this communication should be directed to David Saunders at telephone number (703) 308-3976.

D. Saunders:jmr

November 7, 2002

David A Saunders

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PRIMARY EXAMINER
ART UNIT ~~182~~ 1644